thereof (i.e., IL-15 mutein) either of which is conjugated to a chemical group that sterically interferes with the ability of IL-15 to transduce a signal though the IL-15 receptor complex wherein the antagonist is still capable of binding to the complex. The invention is therefore recited in an alternative form or Markush-type form with respect to the IL-15 limitation. According to MPEP 803.02:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. (emphasis added)

MPEP 803.02 also further states that, citing *In re Harnisch*, it is improper for the PTO to refuse examination that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. According to the MPEP the unity of invention component can be determined in a two-step test: first, whether the alternative members share a common utility; second, whether they share a substantial structure essential to that utility. Applicants respectfully submit that the members recited in the instant claims, IL-15 or a mutein thereof, do not lack the unity of invention as they meet the *Harnisch* test: they share a common utility (i.e., as an IL-15 antagonist) and a structural feature, which is a conjugate comprising an IL-15 or a mutein thereof and a chemical group that sterically interferes with the ability of IL-15 to transduce a signal though the IL-15 receptor complex.

Applicants also respectfully submit that examining both Group I (where IL-15 is native) and Group II (where IL-15 is a mutein) would not place a search burden on the Examiner, whether the search is conducted based on sequence and/or keywords. Since the IL-15 members, including IL-15 and muteins thereof, as claimed are so related to each other, in structure as well as in subject matter for search, a search for one would necessarily uncover the other. Regarding sequence-based search, it is unlikely that a search for SEQ ID NO: 2 (native IL-15 amino acid sequence) would not uncover a variant thereof such as a mutein IL-15. Likewise, a literature or patent search based on keywords, such as IL-15 antagonist, IL-15 conjugate, signal transduction inhibitor, etc., would uncover publications relating to IL-15 or its variations.

The Examiner also alleges that Claim 26 is not a linking claim, citing that the members in the claims are not "equivalent species" and even equating them to the like of a Markush group that consists "of an antibody, bowling ball and a golf ball." Applicants submit that the relationship among the species of claim 26 are nowhere close to that as characterized by the Examiner. To the contrary, they share a common utility and common structure that satisfies the requirement of the *Harnisch* test as discussed above.

Applicants thus respectfully request the Examiner to reconsider the restriction requirement. In the event that the Examiner would not withdraw the restriction requirement, Applicants further submit that Group I and Group II should be rejoined for this examination. In the further event that the Examiner would not rejoin Group I and Group II, Applicants further submit that they should be subjected to an Election of Species requirement.

Applicants note that Claim 42, which the Examiner has not assigned to any of the Groups, should be examined along with Group I as it depends from Claim 41 of Group I.

- Claims 26, 27, 35-38, 40, 41, 43 and 46 are rejected under 35 U.S.C. §112, first paragraph

The Examiner rejected Claims 26, 27, 35-38, 40, 41, 43 and 46 under 112/1, written description, because, as the Examiner alleges, "recitation of antagonist of IL-15 alone is insufficient to describe the genus," that "the disclosure fails to describe the common attributes or characteristics that identify members of the genus," and therefore Applicants were not in possession of the "claimed genus." (page 4, second full paragraph). The Examiner also cites *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991) to support his statement that "[t]he protein itself is required." (page 4, last full paragraph). The Examiner also directs Applicants to the Written Description guideline, which is used as a training material for the Examining corps. Applicants respectfully traverse this rejection on the grounds that Applicants have satisfied the written description requirement under 112/1.

First, the instant claims do not recite antagonist of IL-15 "alone," as the Examiner alleges. The claims recite an IL-15 antagonist in the preamble, following in the body that the antagonist comprises (1) an IL-15 or a mutein thereof, (2) that the IL-15 or the mutein thereof is conjugated to a chemical group that sterically interferes with signal transduction by IL-15, and (3) that the antagonist is capable of binding to the IL-15 receptor complex. Each and every limitation in the claims is fully supported by the specification: Not only IL-15 is a well characterized cytokine (the Examiner is referred to Giri et al. and Grabstein et al.), the specification provides a description of IL-15 and its mutein (e.g., at page 5, lines 16-22), the native amino acid sequences (SEQ ID NO: 1, for simian, and SEQ ID NO: 2, for human) and even the mutated sequences (i.e., mutein) (page 5, lines 9-14; paragraph bridging pages 10 and 11; Example 1). The conjugates of IL-15 or its mutein are described and taught throughout the specification, e.g., mature IL-15 conjugated with PEG or other chemical moieties (page 11, lines 2-27; Example 3).

Secondly, the "common attributes or characteristics that identify members of the genus" are fully described in the specification. The Examiner is directed to, among others, page 5, lines 9-14, where IL-15 and its muteins are described in term of amino acid sequence, and to the paragraph bridging pages 2 and 3, where the conjugates are described. Applicants therefore submit that "members of the genus" are fully described in the Specification.

Third, Applicants respectfully submit that *Fiers* is not applicable to the instant case, with respect to the written description requirement decision, for the reasons that the facts in *Fiers* are different from the instant case. In the instant case, the limitation with respect to IL-15 and its muteins are adequately described in the specification; that is, it discloses the amino acid sequence of IL-15 and how to make a mutein thereof including specific amino acid sequence for the latter (See pages 5 to 8 for example). In *Fiers*, the disclosure was found not satisfying the written description requirement because the specification only describes how to make the DNA whereas it is the DNA *per se* is claimed. Applicants also submit that *Amgen* is not applicable to the instant case, for the simple reason that the issues in *Amgen* involve, with respect to 112/1, only enablement and best

mode requirements. Since the instant rejection is a "written description rejection," as set forth by the Examiner at the outset of this objection/rejection (page 4, line 2), not a rejection on the grounds of non-enablement or failure to provide best mode, Applicants respectfully submit that citing *Amgen* to support the basis for the rejection is improper.

Finally, with respect to the Office's written description guideline, Applicants submit that the instant case satisfies the guideline. Since the Examiner was not specific in his rejection, e.g., no specific Examples in the guideline was cited, Applicants can only guess what Example(s) the Examiner was referring to. The closest Example from the guideline that Applicants suspects the Examiner was referring to is Example 13 ("Protein Variant"). As is the case with *Fiers* and *Amgen* as discussed above, Applicants respectfully submit that the Examiner has again ignored the difference in the facts as represented in each situation. Specifically, the facts between Example 13 and the instant are not similar. The specification of Example 13 "states that the invention provides variants of SEQ ID NO: 3 having one or more amino acid substitutions, deletions, insertions and/or deletions. No further descriptions of the variants is provided." (page 50, lines 6-9). In the instant case, however, both the IL-15 (and mutein thereof) and the chemical moiety (which sterically interferes with IL-15 signal transduction) limitations were not only adequately described but also provided with a representative number of species and with specific examples. See pages 5-9, for example.

Applicants therefore believe that the Specification conveys with reasonable clarity to one skilled in the art that Applicants were in possession of the antagonists as claimed. The written description requirement is thus satisfied. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). It thus follows that the Examiner has not established the initial burden of establishing a *prima facie* case of lack of written description by presenting evidence and reasons why one skilled in the art would not recognize in the disclosure a description of the invention as defined by the claims. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996). In the event that the Examiner is not in agreement with Applicants' position, Applicants request that the Examiner be more specific in stating and describing the basis of the objection under 112/1, written description, rather than using general language as it is the case in the instant Office action, so that Applicants have an opportunity to address the basis of the objection more specifically.

For at least the reasons discussed above, Applicants respectfully request reconsideration and withdrawal of this rejection.

- Claims 26-29, 35-38, 40, 41, 43, 44 and 46 are rejected under 35 U.S.C. §103

The Examiner rejected Claims 26-29, 35-38, 40, 41, 43, 44 and 46 as being unpatentable over Giri et al. ("Giri") and Grabstein et al. ("Grabstein") in view of Ferrara et al. ("Ferrara") and Hakimi et al. ("Hakimi"). Applicants respectfully traverse this rejection on the grounds that the combination of the cited references does not suggest Applicants' invention.

Applicants' invention is directed to an antagonist of IL-15 activity comprisng IL-15 or a mutein thereof conjugated to a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex and wherein the antagonist is still capable of binding to the receptor complex.

Applicants submit that none of the cited references, either alone or combined, teaches or suggests the claimed invention.

To establish a case of *prima facie* obviousness, a combination of references must suggest to an ordinary skill in the art that the artisan should make the claimed invention, and even if it does it must reveal to the artisan a reasonable expectation of success. *In re Vaeck*, 20 USPQ 1438, 1442 (Fed. Cir. 1991). Furthermore, both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Moreover, the Federal Circuit has cautioned that, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). In the present case, the combination of the cited references does not in fact teach or suggest an antagonist of IL-15 which comprises IL-15 or a mutein thereof conjugated to a chemical group, e.g., PEG, that sterically interferes with signal trasnduction of IL-15 through the IL-15 receptor complex and which is still capable of binding to the receptor.

Giri teaches that IL-15: (1) shares bioactivities with IL-2 but no sequence homology to IL-2; is not involved in binding with the α subunit of receptor of IL-2 (IL-2 receptor); requires both the β and γ subunits of IL-12 receptor for binding and signaling (Abstract). Giri also implies that there is an additional, specific, yet unidentified component for binding IL-15. Giri thus neither teaches nor suggests an IL-15 antagonist. Even assuming *arguendo* that Giri may teach or suggest making IL-15 antagonist, Giri does not teach or suggest the antagonists as claimed, which comprises an IL-15 conjugated to a chemical group that interferes with the ability of IL-15 to transduce through the IL-15 receptor complex.

Grabstein teaches a novel cytokine, IL-15, that interacts with the β chain of IL-2 receptor, including its primary structure, a length of 162 amino acids of which the first 48 residues are of the leader sequence. Grabstein thus neither teaches nor suggests an IL-15 antagonist. Even assuming *arguendo* that Grabstein may teach or suggest making IL-15 antagonist, Grabstein does not teach or suggest the antagonists as claimed, which comprises an IL-15 cojugated to a chemical group that interferes with the ability of IL-15 to transduce through the IL-15 receptor complex.

Ferrara teaches that antibodies directed against the IL-2 receptor may be useful in clinical marrow transplantation as they reduce the severity of GVHD when injected into patients. Ferrara thus neither teaches nor suggests IL-15, let alone an IL-15 antagonist. Even assuming *arguendo* that Ferrara may teach or suggest making an IL-15 antagonist because it teaches what may be considered as an IL-2 antagonist, it does not teach or suggests the antagonists as claimed, which comprises an IL-15 conjugated to a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex. In other words, the type of antagonist that may be taught or suggested by Ferrara, an antibody directed against the receptor, is distinct from that as instantly claimed, an IL-15 conjugated to a chemical group that interfers with IL-15 signal transduction through the IL-15 receptor complex.

Hakimi discloses physiologically active protein conjugates, in which unique linkers are used to connect the various free amino groups in the protein to PEG (col. 1, lines 51 to 56). Hakimi also dicloses an IL-1

receptor antagonist (IL-1ra) and an IL-1 conjugated to PEG (col. 2, lines 3 to 6). Hakimi also discloses that a PEG-conjugated IL-1ra with an apparent molecular weight of 37 Kd retains binding within 6-fold relative to IL1-ra, and another one with an apparent molecular weight of 48 Kd which substantially loses its binding to the IL-1 receptor (col. 17, lines 31 to 41). Hakimi thus neither teaches nor suggests an IL-15 antagonist as claimed.

Thus, none of the cited references, taken alone or in combination, teaches or suggests an antagonist of IL-15 activity having the limitations of Applicants' claimed invention. Giri and Grabstein involve only in the isolation and characterization of IL-15. Ferrara and Hakimi do not even mention IL-15 or IL-15 receptor complex, let alone an antagonist having the limitations as claimed. The only reference that teaches antagonist is Ferrara, which teaches an IL-2 monoclonal antibody to treat GVHD. The instant antagonist, however, is not an antibody-based molecule but a conjugate comprising IL-15 or a mutein thereof and a chemical group. Even if a combination of these references may suggest to arrive at the antagonist as claimed, it provides no reasonable expectation of success in doing so.

Each antagonist is a unique chemical entity, each comprising its own cytokine (e.g., IL-15, IL-2, or IL-1ra) and the type of chemical conjugation. Furthermore, with respect to cytokine and receptor interaction, each is also unique with binding and signal transduction domain(s). Because each cytokine and its receptor are unique with respect to binding and signal transduction, and even with the knowledge of chemical conjugation as disclosed in Hakimi, it does not simply mean that an antagonist to one cytokine (e.g., an IL-1ra antagonist) would render obvious an antagonist to another cytokine (e.g., IL-15). The cited references provide, at best, an invitation to experiment – a general incentive and a general approach in antagonizing signal transduction (as underlined in the quote from the Examiner's "motivation statement below).

> "It would have been prima facie obvious to have taken the IL-15 as taught by Giri et al or Grabstein et al and to have conjugated the IL-15 to PEG as taught by Hakimi et al to create such an antagonist in view of the teaching by Ferrara et al that GVHD severity was reduced by inhibiting the activity of IL-2 and the teaching by Giri et al that IL-15 has shared bioactivities with IL-2." (page 7) (emphasis added)

Applicants note that Hakimi does not teach or even suggest to conjugate IL-15 to PEG, as the Examiner characterizes the reference in the "motivation" statement. Furthermore the instant claims are directed to a product *per se*, an IL-15 antagonist, not a process for making an IL-15 antagonist which the Examiner appears to examine.

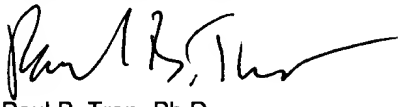
For at least the reasons discussed above, Applicants respectfully request reconsideration and withdrawal of this rejection.

- **Conclusion**

Applicants believe that the foregoing amendment and remarks are fully responsive to the Examiner's outstanding rejections and place the pending claims in condition for allowance. Applicants also request the Examiner to reconsider and withdraw the restriction requirement for the reasons set forth in the foregoing

remarks. If a telephone interview would be helpful in advancing the prosecution of this application the Examiner is invited to contact the undersigned.

Respectfully submitted,



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Appendix A

MARKED-UP VERSION TO SHOW CHANGES MADE

Claim 26. (Amended) An antagonist of interleukin-15 (IL-15) activity comprising IL-15[,] or a mutein thereof [of IL-15], conjugated with a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex, wherein said antagonist is capable of binding to said IL-15 receptor complex.

Claim 27. (Amended) The antagonist of claim 26 wherein said IL-15 is native [IL-15 is conjugated with a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex].

Claim 28. (Amended) The antagonist of claim 27 wherein the native IL-15 [has] comprises the sequence of amino acids 49-162 of SEQ [ID:1] ID NO: 1 or 49-162 of SEQ [ID:2] ID NO: 2.

Claim 29. (Amended) An antagonist of interleukin-15 (IL-15) activity comprising native IL-15 [having] comprising the sequence of amino acids 49-162 of SEQ [ID:2] ID NO: 2 conjugated with a chemical group that sterically interferes with the ability of IL-15 to transduce a signal through the IL-15 receptor complex, wherein said antagonist is capable of binding to said IL-15 receptor complex.

Claim 35. (Amended) The antagonist of claim 26 wherein [the IL-15 or mutein of IL-15 is covalently bonded to a large inert moiety] the chemical group is selected from the group consisting of PEG, mPEG, PVP, dextran, PVA, poly amino acids, albumin, and gelatin.

Claim 36. (Amended) The antagonist of claim 35 wherein the [large inert moiety] chemical group is selected from the group consisting of PEG, PVP, and dextran.

Claim 37. (Amended) The antagonist of claim 36 wherein the [large inert moiety] chemical group is PEG having a molecular weight of between about 1,000 and about 20,000.

Claim 38. (Amended) The antagonist of claim 28 wherein the IL-15 is covalently bonded to PEG having a molecular weight of between about 1,000 and about 20,000.

Claim 40. (Amended) The antagonist of claim 37 wherein the PEG has a molecular weight of about 5,000.